REMARKS

STATUS OF THE CLAIMS

Claims 1-3, 8 and 15 were on appeal after being finally rejected under 35 U.S.C. §§ 103 and 112, first paragraph. The Office has reopened prosecution and mailed a non-Final Office Action setting forth new grounds of rejection. Applicants hereby elect to file a reply under 37 C.F.R. § 1.111 to address the new grounds of rejection.

Claim 1 has been amended as shown above to recite known cancer antigens. Support for the amendments can be found throughout the specification as filed, for example on page 5, line 27 to page 6, line 1. Thus, claims 1-3, 8 and 15 are pending as shown above.

REJECTIONS WITHDRAWN

Applicant gratefully acknowledges withdrawal of the previous rejection of claims 1-3, 5 and 8 under 35 U.S.C. § 112, first paragraph as well as withdrawal of the rejection of claims 1-3, 8 and 15 under 35 U.S.C. 35 U.S.C. § 103(a) over Hseih-Ma, Weiner or Ring in view of Fanger. (Office Action, paragraphs 5 and 6).

Applicants request clarification as to whether the rejection of claims 1-3, 8 and 15 under 35 U.S.C. 35 U.S.C. § 103(a) over Hseih-Ma, Weiner or Ring in view of Fanger and in further view of the U.S. Patent No. 6,054,561 (hereinafter "the '561 patent") is withdrawn or maintained. Paragraph 7 of the Office Action indicates the rejection is maintained. However, the paragraph falls under the heading of "Claim Rejections Withdrawn." For the sake of completeness, Applicant addresses the rejection again below.

35 U.S.C. § 103

Should the rejection of claims 1-3, 8 and 15 as allegedly obvious Hseih-Ma, Weiner or Ring in view of Fanger and in further view of the '561 patent be maintained, Applicant reiterates the fact that there is no teaching, suggestion or motivation within the cited references to support the rejection made by the Examiner.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The reference must teach all the limitations of the claimed invention and, moreover, suggests the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of along sought and difficult scientific goal was obvious" and *In re Laskowski,* 10 USPQ2d 1397, 1399

(Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.") Thus, the Board has previously acknowledged that disclosure of an isolated protein does not necessarily render obvious the same recombinantly produced protein. *See, e.g., Ex parte Goeddel,* 5 USPQ2d 1449 (BAPI, 1987).

Claims 1-3, 8 and 15 are all directed to methods of inducing **antibodies** to cancer antigens by administering the bispecific antibodies as claimed. Nowhere do any of the references teach or suggest the induction of antibodies against cancer antigens using bispecific antibodies as claimed. Nor do these references provide any motivation or suggest the desirability of such methods. The failure of the cited references to suggest the claimed methods is also laid out in the Wong Declaration, filed April 1, 2003. There is simply no basis in the references for making an obviousness rejection and Applicant submits that it should be withdrawn. As Dr. Wong stated:

> 12. It is further my opinion that the references cited in the Final Office Action do not describe, demonstrate or suggest the claimed methods. The application at issue discloses and claims methods of inducing an antibody response to a cancer antigen using a bispecific antibody. The bispecific antibody itself recognized FcγRIII and the cancer antigen. There is no disclosure in any of Hseih-Ma, Weiner, Ring, Fanger of Snider that would lead any scientist working in this area to conclude that bispecific antibodies would be useful in generating antibodies against cancer antigens. The fact that bispecific antibodies can have induce such antibodies was, in fact, a surprising finding made by the present inventors *after* all of the references were published, as noted on page 6, lines 24-28 of the specification:
>
> > It has now been found that administration of bispecific antibodies which recognize and bind FcγRIII and a second antigen can promote an immune response in humans to the second antigen. The immune response includes the formation of antibodies to the second antigen.
>
> Nowhere do any of the references report or test antibody production in response to the precisely-claimed subject matter. Accordingly, I do not believe that any combination of the cited references would lead one of skill in the art to the methods claimed by Applicant.

Thus, the Examiner has improper ignored the requirement that the claimed methods result in the induction of antibodies to the cancer antigen recognized by the second binding site of the bispecific antibody. Functional limitation must be evaluated and considered, just like any other

limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. (M.P.E.P. 2173.05(g) Functional Limitations, Eighth Edition). There is nothing inherently wrong with defining some part of an invention in functional terms and functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). Indeed, where the particular intended result (in this case production of antibodies to specified antigens) is a limitation of the pending claims it is entirely relevant to patentability. Accordingly, the requirement in these claims regarding the nature of immune response generated is entirely relevant the obviousness inquiry and establishes, along with the other evidence of record, that the claims are patentable over any combination of the cited references.

Here, the claims on appeal expressly recite that the claimed methods must result in the production of antibodies directed against the cancer antigen and, hence, this limitation is relevant to patentability. It is unacceptable for the Examiner to ignore this limitation and assert that any art related to the making or using of bispecific antibodies is relevant, much less than these references render the particularly claimed invention unpatentable. Likewise, the Examiner cannot ignore the legal axiom that obviousness cannot be based on what was allegedly inherent. Thus, when the proper legal standards of obviousness are applied, it is clear that the claimed methods, drawn to production of antibodies using bispecific antibodies, are in no way obvious over the cited references.

There is, in sum, no motivation provided by the cited references to arrive at methods of inducing antibodies to cancer antigens as recited in the appealed claims. The steps and results of the claimed methods are precisely defined -- in the claims themselves, not in the references. None of the references teach that antibodies to cancer antigens would be induced by administration of the claimed bispecific antibodies. Therefore, Applicant respectfully requests that the rejection of these claims as allegedly obvious over the cited references be withdrawn, and that these claims be allowed.

35 U.S.C. § 102

The pending claims are newly rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,959,084 (hereinafter "the '084 patent"). In addition, the claims are newly rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Weiner.

Applicant traverses the rejection.

The pending claims are not anticipated by the '084 patent or by Weiner because these references do not disclose each and every element of the claimed methods. The claims are

directed to methods of inducing antibody production against an antigen recognized by one of the binding sites of a bispecific antibody. The '084 patent and Weiner are silent as to production of antibodies. Instead, these references disclose that administration of bispecific antibodies kills cancer cells by "lysis through cross-linking of the target cell with effector cells expressing hFcγRIII." *See,* col. 25, lines 17-19 of the '084 patent and the 1st sentence of the Abstract. This is unrelated to methods of producing antibodies to the second antigen.

Accordingly, these references do not anticipate the pending claims and withdrawal of the rejections is requested.

35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT

A. CLAIMS 1-3 AND 15

Claims 1-3 and 15 are newly rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification as filed. (Office Action, paragraph 10, page 5). It is maintained that "the specification, while being enabling for methods comprising the administration of bispecific antibodies comprising a first binding site that binds to FcγRIII and a second binding site that binds to the antigens c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein, does not reasonably provide enablement for methods comprising the administration of bispecific antibodies comprising a first binding site that binds to FcγRIII and a second binding site that binds to an antigen that is solely characterized as an antigen the binds to a monoclonal antibody produced by a hybridoma cell." *Id.* Simply put, it is alleged that the second antigen is not adequate described by a structure or a combination of physical and chemical properties. (paragraph 10, page 7).

To the extent that the foregoing amendments to claim 1 do not obviate the rejection, Applicant traverses.

As a threshold matter, Applicant reiterates that the claims are directed to methods of inducing antibody production using bispecific antibodies that are clearly set forth in the specification as filed. Thus, the specification is not required to teach the structure of the antigen(s) recognized by the bispecific antibody in order to establish enablement. What is required is that the specification teach one of skill in the art how to make and use bispecific antibodies to induce antibody production, as claimed. For the reasons of record and those reiterated below, the specification satisfies this requirement.

The bispecific antibodies used in the claimed methods are amply defined in the specification as filed. In addition to disclosing the structure of various antigens bound by these bispecific antibodies (*e.g.,* FcγRIII, c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein), the

specification also clearly sets forth how to make a bispecific antibody that includes, as its second binding site, a binding site derived from one of the recited monoclonals.

Therefore, when properly construed, it is plain that the specification as filed fully enables one of the skill in the art to practice the claimed methods using bispecific antibodies with the claimed structure and function. *See also,* Appeal Brief, filed November 12, 2003; and pages 9, line 12-28 describing generation of bispecific antibodies, pages 24-29 describing testing of subjects for antibody production. Working examples, detailing each claimed step, are set forth. Furthermore, Dr. Wong, an immunologist working in the field of bispecific antibodies, reviewed the specification and unequivocally concluded that the claims were not unduly broad and, in fact, the specification provided ample guidance to the skilled worker to practice the methods as claimed:

> 7. In December 1994, the quantity of experimentation required to make bispecific antibodies that recognized FcγRIII and a cancer antigen was quite low. At the time of filing and as described in the specification, FcγRIII was a well-characterized isoform of the CD16 cell surface receptor. (*See,* for example, page 10, lines 6-16). One working in this field could have readily selected suitable cancer antigens, for example as described in detail on pages 17-20. Also well known at the time of filing were techniques of producing bispecific antibodies and these standard procedures are described throughout the specification as filed, for example, on page 9, line 12-28 (including the references cited therein). Based on these extensive teachings regarding each of the antigens recognized by the claimed bispecific antibody and, additionally, the extensive teachings regarding production of bispecific antibodies, it is evident that a skilled worker would have easily produced bispecific antibodies which bound both FcγRIII and a cancer antigen. Thus, it is clear from the specification that 2B1 is merely one example of a hybrid hybridoma capable of producing bispecific monoclonal antibody. Therefore, it is my opinion that it would have required only routine experimentation for the skilled worker to make a bispecific antibody that recognized FcγRIII and a cancer antigen, as recited in the pending claims.

Thus, the specification's disclosure fully enables the methods of claims 1-3 and 15 throughout their scope and withdrawal of this rejection is requested.

B. CLAIM 15

Claim 15 is also separately (and newly) rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification as filed. (Office Action, paragraph 11, page 8). The

Office Action asserts that claim 15 reads on "prophylactic methods of tumor vaccination," which are alleged not be enabled by the specification as filed. *Id.*

Applicants traverse the rejection and supporting remarks.

As the Examiner correctly notes, an enablement inquiry must begin with interpretation of the scope of the claims. *See, In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988). In the pending case, however, the Examiner errs in interpreting the pending claims to cover methods of preventing cancer. There is no requirement in claim 15 that the subject that the antibodies produced "prevent" cancer. All that is required is that antibodies to the second antigen be produced. Thus, claim 15 is not drawn to methods of preventing cancer, but, instead, is directed to a method of generating antibodies in a subject that does not itself have the antigen. These methods may or may not be protective against cancer.

Despite the fact that the method is not required to "prevent cancer," Applicant notes that the claimed method is in fact limited in ways not noted by the Office. In particular, claim 15 clearly requires (1) that the first binding site of the bispecific antibody recognize FcγRIII; (2) the second binding site recognize one of the specified cancer antigens; and (3) that the second binding site is obtained from one of the specified monoclonals. Simply put, claim 15 is directed to a method of inducing antibody production using particular bispecific antibodies. When properly interpreted, Applicant submits that there is no question that the specification as filed fully enables claim 15 throughout its scope.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). Accordingly, in the pending case, Applicant is in no way required to show prevention of cancer in a subject. All that is required is that the specification teaches a skilled practitioner how to make a bispecific antibody as set forth, administer the bispecific antibody and evaluate antibody production in the subject. As noted above, the specification more than satisfies this requirement, as it clearly sets forth how to make bispecific antibodies as claimed, administer these antibodies to a subject and evaluate antibody production. The skilled artisan could readily select any second binding site from the recited monoclonals in which the practitioner is presumably already interested, according to the disclosure, and test whether or not antibodies are produced, again according to the disclosure. If no antibodies are produced in the subject, the selected bispecific antibody does not fall within the scope of the claims. Accordingly, to the extent that the foregoing amendments do not obviate this rejection, Applicants submit that the specification fully enables methods of inducing the production of antibodies in a subject, regardless of the subject's cancer "status."

Thus, when the *Wands* factors are considered, the claims as presently presented are of reasonable scope and are fully enabled by the specification as filed. Accordingly, withdrawal of this remaining rejection is respectfully requested.

35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 1-3 and 15 are newly rejected under 35 U.S.C. § 112, first paragraph as allegedly not described by the specification as filed. (Office Action, paragraph 12). It is maintained that the specification does not describe adequate structural, physical or chemical characteristics of an antigen and that the term "derived from" is "interpreted broadly to mean that the binding site may have as little as one amino acid in common with the referenced monoclonal antibody binding site." *Id.*

Applicants traverse the rejection and supporting remarks.

The pending claims are drawn to methods of inducing antibody production using bispecific antibodies. The bispecific antibodies are precisely defined in the claims, either by a known and characterized antigen to which they bind (*e.g.*, FcγRIII, cerbB-2, HMW mucin, HMW mucin II, p-glycoprotein) or by the nature of the binding site (obtained from a specified monoclonal). The specification clearly describes all steps of the claimed methods, including the structure of the bispecific antibodies used in the methods.

With regard to the term "derived from," Applicant directs the Examiner's attention to page 10, lines 22-27 of the specification where it states:

> The term "binding site derived from a monoclonal antibody" as used herein means a binding site in a second antibody or antibody fragment having the same or homologous CDRs as the monoclonal antibody. Homologous CDRs should be understood to include one set of CDRs from an antibody in which the primary sequence of each CDR is at least 50% identical to the antibody and the binding site formed by these CDRs binds to the same epitope as the monoclonal antibody.

In other words, the claimed methods will not make use of bispecific antibodies having "as little as one amino acid in common" with the referenced monoclonal antibody binding site, as alleged in the Office Action. Rather, the bispecific antibodies used in these methods are clearly described in terms of structure (at least 50% homology to CDR of monoclonal antibody from which they are obtained) and function (bind to the same epitope as the monoclonal antibody from which they are obtained). Thus, the structural, physical, chemical and functional

characteristics of the second binding site of the bispecific antibody is more than amply described in the specification as filed.

In sum, the specification as filed clearly describes the methods as claimed and withdrawal of this rejection is in order.

CONCLUSION

In view of the foregoing, Applicant submits that the claims are now in condition for allowance and requests early notification to that effect.

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